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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/203,768	12/02/98	WATKINS J	P-IX-2947

023601
CAMPBELL & FLORES LLP
4370 LA JOLLA VILLAGE DRIVE
7TH FLOOR
SAN DIEGO CA 92122

HM12/0818

EXAMINER	
HELMS,L	
ART UNIT	PAPER NUMBER
1642	11

DATE MAILED: 08/18/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/203,768	Watkins et al
Examiner	**Group Art Unit**
Larry R. Helms Ph.D.	1642

☒ Responsive to communication(s) filed on *19 Jun 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-46* is/are pending in the applicat

Of the above, claim(s) *7-46* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-6* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4 and 7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-6, in Paper No. 9 is acknowledged. The traversal is on the ground(s) that "Group I be examined together with claims of Groups VII and XII, and similarly, that the tripartite claims of Groups III, VIII, and XIII; Groups IV, IX, and XIV; Groups V, X, and XV; and Groups VI, XI, and XVI each be rejoined into single Groups." Further the traversal is on the grounds that "Moreover, a search of the method of Groups VII or XII would necessarily reveal the recited antibody or functional fragment of Group I.". This is not persuasive. As to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. As stated in the previous Office Action the antibodies of Groups I, and III-VI can be used in a materially different method than that claimed in Groups VII-XVI such as for immunopurification of the specific antigens. Thus, Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. This application contains claim drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. Claims 7-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

4. Claims 1-46 are pending.

Claims 1-6 are under examination.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-6 are indefinite for reciting in claims 1 and 6 "substantially" for the exact meaning of the term is not clear. It is not clear if the CDR comprises the entire sequence of SEQ ID NO: 2 or 4 or what amino acid residues contained in the CDR are encompassed by the term.

b. Claims 1-6 are indefinite for reciting "amino acid sequence of a CDR" in claims 1 and 6 for the exact meaning of the phrase is not clear. It is not clear what definition is used to define the CDR. In the specification on page 9 three different CDR definitions are given, each different.

c. Claims 1 and 3-6 are indefinite for reciting "functional fragment" for the phrase is not clear. It is not clear what function is defined in the claims.

d. Claim 1 is indefinite for reciting the term "having" for the exact meaning of the term is not clear. Does the term mean consisting of or comprising?

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a human monoclonal antibody and antigen binding fragments thereof comprising a heavy chain amino acid sequence of SEQ ID NO:2 and a light chain comprising amino acid sequence of SEQ ID NO:4, wherein said human monoclonal antibody further comprises a label which is a cytotoxic or cytostatic agent, and compositions comprising such, does not reasonably provide enablement for a human monoclonal antibody which does not contain a full set of six CDRs or a functional fragment thereof or a CDR alone which would not bind antigen, further comprising a label and pharmaceutical compositions comprising such. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

a. Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of

the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

b. The claims are broadly drawn to a human monoclonal antibody which comprises at least one CDR of SEQ ID NO:2 or SEQ ID NO:4 or a CDR alone which would not bind antigen and functional fragments thereof and pharmaceutical compositions comprising such.

c. The specification teaches SEQ ID NO:2 is the amino acid sequence of the VH of the monoclonal antibody produced by LH11238 cell line and SEQ ID NO:4 is the amino acid sequence of the VL of the monoclonal antibody produced by LH11238 cell line (see page 16, lines 13-15). The specification teaches the LH11238 antibody displayed surface staining and the LH11238 antigen is present on the plasma membrane and in the lysosomes of H3464 cells (see page 55-56). The specification fails to enable an antigen binding fragment or an antibody which does not contain a full set of six CDRs or a CDR of SEQ ID NO:2 or 4 or any fragment of the LH11238 antibody or pharmaceutical compositions comprising such.

d. The claims are not commensurate in scope with the enablement provided in the specification. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact

residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional human antibody can be obtained with at least one CDR. As evidenced by Adair et al. (WO 91/0996) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (p. 4). Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88)

demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).
One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed.

e. Claim 5 is drawn to a pharmaceutical composition comprising the antibody of claim 1. Enablement of a "pharmaceutical composition" is considered to rest on a teaching of in vivo administration for purposes consistent with the intended use disclosed in the specification. The disclosed intended use for the claimed pharmaceutical composition is for the treatment of cancer. Thus, the nature of the invention is a therapeutic composition used in the treatment of cancer.

f. Although the specification discloses the claimed composition, and general methods for formulating compositions in pharmaceutically acceptable carriers, there is insufficient guidance which would enable one skilled in the art to use the claimed compositions for their intended purpose, viz., for the treatment of cancer.

g. At the time the invention was made, pharmaceutical compositions comprising the claimed antibodies were not routinely used for the treatment of cancer. The specification lacks guidance by way of general methods or working examples which teach an "effective amount" of the polypeptide which would be used for this purpose. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art, such as cancer therapy. Further, it is not routine in the art of cancer therapy to use compositions analogous to the claimed

compositions for this purpose. Accordingly, there is no objective basis upon which the skilled artisan would reasonably be able to determine or predict an amount of the claimed composition effective for its intended use.

h. Amending the claim to remove the term "pharmaceutical" prior to the term "composition" would be sufficient to obviate this portion of the rejection.

I. Therefore, in view of the lack of predictability in the art as evidenced by Rudikoff et al, Panka et al, Adair et al, and Amit et al and the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Conclusions

9. No Claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. Any inquiry of a

general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

Sheela J. Huff

SHEELA HUFF
PRIMARY EXAMINER